



Research Article

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Preliminary phase I/II multicenter trial of combined fuzuloparib and realgar-indigo naturalis formula in recurrent platinum-resistant ovarian cancer: clinical and molecular insights

Junfen XU^{1,2*}, Shaoshuai TANG^{3*}, Tingting CHEN^{1,2}, Yumei ZHOU¹, Changkun ZHU¹, Shan PAN⁴,
Bairong XIA⁵, Yuanming SHEN^{1,2}

¹Department of Gynecologic Oncology, Women's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, Zhejiang, China

²Zhejiang Key Laboratory of Precision Diagnosis and Therapy for Major Gynecological Diseases, Women's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, Zhejiang, China

³State Key Laboratory of Genetic Engineering, Institutes of Biomedical Sciences, School of Life Sciences, Human Phenome Institute, Fudan University, Shanghai 200032, China

⁴Department of Gynecology, Jiaxing Women and Children's Hospital Wenzhou Medical University, Jiaxing 314051, China

⁵Department of Gynecological Oncology, Anhui Provincial Cancer Hospital, Hefei 230031, Anhui, China

Abstract: This study evaluated the efficacy, safety, and molecular correlates of combined treatment with fuzuloparib and realgar-indigo-naturalis formula (RIF) in patients with platinum-resistant ovarian cancer (PROC). Fourteen heavily pretreated patients received fuzuloparib (150 mg BID) plus RIF; RIF was escalated from 1.62 g TID to 2.43 g TID during the initial three-patient dose-escalation phase, after which the other 11 patients received the recommended phase-II dose of 2.43 g TID. The objective response rate (ORR) was 14.3%, with two patients achieving a partial response and 35.7% of patients achieving a CA125 response. The median progression-free survival (mPFS) and overall survival (mOS) were 2.25 and 9.5 months, respectively. Clinical responses were evident irrespective of BRCA status, with a trend toward longer survival among HRD-positive patients. The combination was generally well tolerated, with adverse events predominantly classified as grade 1-2. Integrated proteomic and metabolomic profiling identified pathways related to detoxification, lipid metabolism, and serotonin signaling as potential molecular correlates of poor response, whereas longitudinal profiling revealed dynamic immune and metabolic changes during disease progression. Given the small, clinically heterogeneous, and heavily pretreated cohort, these preliminary efficacy findings should be interpreted with caution. Overall, fuzuloparib plus RIF demonstrated clinical feasibility and preliminary antitumor activity, warranting further evaluation in larger, prospective cohorts.

Key words: Fuzuloparib; Realgar-indigo naturalis formula (RIF); Platinum-resistant ovarian cancer; homologous recombination deficiency; Proteomics and metabolomics

1 Introduction

Ovarian cancer is the third most common and the most lethal gynecologic malignancy worldwide (Bray et al., 2024). In 2022, approximately 324,603 new cases and 206,956 deaths from ovarian cancer were reported

✉ Junfen XU, xjfzu@zju.edu.cn

✉ Yuanming SHEN, 5312010@zju.edu.cn

* The two authors contributed equally to this work

Junfen XU, ORCID: <https://orcid.org/0000-0002-2377-0775>

Yuanming SHEN, ORCID: <https://orcid.org/0000-0002-0474-3472>

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worldwide, including approximately 61,060 new cases and 32,646 deaths in China (<https://gco.iarc.who.int/today>) (Bray, et al., 2024; Han et al., 2024). For patients with newly diagnosed advanced ovarian cancer, standard treatment consists of primary or interval cytoreductive surgery followed by platinum-based chemotherapy, with or without bevacizumab (Richardson et al., 2023). Although frontline therapy achieves response rates of approximately 75%-80%, approximately 70% of patients with stage III/IV disease experience recurrence within 6 months after completion of platinum-based therapy (Ledermann et al., 2018; Colombo et al., 2019; Yang et al., 2022). The prognosis of patients with advanced-stage disease remains poor, with reported 5-year survival rates of approximately 42% for stage III and 29% for stage IV disease (Torre et al., 2018; Konstantinopoulos and Matulonis, 2023).

Patients with platinum-resistant ovarian cancer (PROC) have limited therapeutic options, with current treatment generally consisting of sequential single-agent non-platinum chemotherapy or enrollment in clinical trials (Ledermann et al., 2013; Davis et al., 2014). According to the 2024 National Comprehensive Cancer Network (NCCN) guidelines, non-platinum regimens, including cyclophosphamide, docetaxel, etoposide, gemcitabine, liposomal doxorubicin, paclitaxel, and topotecan (either alone or combined with the anti-angiogenic agent bevacizumab), provide limited clinical benefit in this context. Reported objective response rates (ORRs) are generally below 12%, while progression-free survival (PFS) is typically less than 4 months and overall survival (OS) is generally less than 12 months (Barber et al., 2013; Pujade-Lauraine et al., 2014; Colombo, et al., 2019). Moreover, these treatments can cause substantial toxicity, resulting in neuropathy, neutropenia, alopecia, or palmar-plantar erythrodysesthesia, which can negatively affect patients' quality of life (Lindemann et al., 2017; Richardson, et al., 2023). Therefore, there is a critical need for effective and tolerable treatment strategies for PROC.

Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors (PARPi), including niraparib, olaparib, rucaparib, and fuzuloparib, have become important targeted therapies for ovarian cancer, particularly in tumors with defects in homologous recombination-mediated DNA repair, such as BRCA1/2 mutations or homologous recombination deficiency (HRD) (Kaufman et al., 2015; Oza et al., 2017; Moore et al., 2019; Li et al., 2021). PARPis have demonstrated substantial clinical benefit, particularly as first-line or platinum-sensitive relapse-maintenance therapy (Kaufman, et al., 2015; Kim et al., 2015; Matulonis et al., 2016; Shoaib et al., 2025). Their activity is closely related to the concept of synthetic lethality, whereby inhibition of PARP-mediated DNA repair preferentially compromises the survival of tumor cells with impaired homologous recombination repair (Coleman et al., 2017; Moore et al., 2018; Gonzalez-Martin et al., 2019; Li, et al., 2021; Disilvestro et al., 2023; Lorusso et al., 2024). However, the efficacy of PARP-inhibitor monotherapy remains limited in platinum-resistant disease, with reported ORRs ranging from 4-13% in patients with HRD-negative or unknown tumors and approximately 10-38% in HRD-positive patients (Gelmon et al., 2011; Moore, et al., 2019; Swisher et al., 2021). These findings highlight the need for combination strategies that could enhance PARP-inhibitor activity and overcome resistance in PROC.

Realgar-indigo-naturalis formula (RIF) is a traditional Chinese oral medicine formulation containing realgar (arsenic sulfide), indigo naturalis (Qing Dai), radix pseudostellaria, and radix salviae miltiorrhizae, and has demonstrated potential antitumor activity (Zhu and Huang, 2014; Zhu et al., 2018; Lou et al., 2020; Ma et al., 2022). Our previous studies showed that arsenic-containing compounds, including those present in RIF, can sensitize homologous recombination-proficient ovarian cancer cells to PARPi, including niraparib, olaparib, and fuzuloparib (Xu et al., 2021). This sensitization is associated with increased DNA damage and enhanced tumorcell apoptosis. We also demonstrated that the combination of RIF with PARPi increased DNA damage, inhibited tumor-cell proliferation, and suppressed tumor growth in ovarian cancer models without significant additional toxicity (Xu, et al., 2021). Consistent with these findings, arsenic combined with olaparib has been reported to overcome platinum resistance in ovarian cancer cells through the induction of apoptosis and ferroptosis (Tang et al., 2022). Together, these preclinical findings provide a rationale for investigating RIF in combination with PARP inhibition in PROC.

In this study, we evaluated the safety, preliminary efficacy, and potential molecular correlates of

fuzuloparib combined with RIF in patients with PROC, using a Phase I/II dose-escalation and expansion design. In addition to assessing the clinical activity and tolerability of this combination, we performed longitudinal plasma proteomic and metabolomic profiling to explore molecular features associated with treatment response, CA125 dynamics, and BRCA/HRD status, with the aim of providing translational insights into potential mechanisms of treatment response and resistance.

2 Materials and methods

Our methods are extensively described in the supplementary materials and methods.

2.1 Study design

This open-label, single-arm, two-stage study was conducted to evaluate the efficacy and safety of a combination treatment of fuzuloparib and RIF in patients diagnosed with platinum-resistant relapsed ovarian cancer. The fuzuloparib used was kindly provided by Jiangsu Hengrui Pharmaceuticals Co., Ltd., China, and RIF was supplied by Tianchang Yifan Pharmaceutical Co., Ltd., China. Typically, standard chemotherapy regimens in these patients result in an ORR ranging from 4% to 16%. We aimed to test the hypothesis that the combination therapy would increase the ORR to 25%. Fourteen patients were enrolled, comprising individuals diagnosed with high-grade serous ovarian cancer. Thirteen were recruited from the Women's Hospital, Zhejiang University School of Medicine, while one was from the Anhui Provincial Cancer Hospital.

2.2 Ethics

The clinical trial protocol received approval from the Institutional Review Boards at both participating sites (Approval numbers: IRB-20200214-R and IRB-2023-47). Written informed consent was obtained from all participants prior to any study procedures. The trial is registered at Clinicaltrials.gov (NCT04518501) and was conducted following the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

3 Results

3.1 Patient characteristics

Between April 20, 2021 and November 10, 2024, a total of 14 eligible PROC patients were recruited from two study sites in China and began treatment at Women's Hospital, Zhejiang University School of Medicine, and the Anhui Provincial Cancer Hospital. The baseline characteristics of the patients are summarized in Table 1. The median age of participants was 58 years (range, 43-74 years). All participants had high-grade serous ovarian cancer, and the majority had primary tumors originating from the ovary (12 patients, 85.7%), while 2 patients (14.3%) had tumors originating from the fallopian tube. Most patients had an ECOG performance status of 0 (11 patients, 78.6%). Among the patients, 4 (28.6%) achieved R0 status with initial surgical treatment, 5 (35.7%) did not achieve R0 status, and 5 (35.7%) did not have a recorded status. All patients had previously undergone platinum-based therapy; 8 (57.1%) had platinum-refractory disease, while 6 (42.9%) had platinum-resistant disease, including 4 (28.6%) who had received more than three lines of platinum-based chemotherapy and 2 (14.3%) who had received seven lines of platinum-based chemotherapy. Furthermore, 13 of 14 patients had not received prior PARPi therapy.

Of the 14 patients, 3 (21.4%) had disease confined to the pelvic region, while 11 (78.6%) presented with extra-pelvic recurrence, including 5 (35.7%) with distant metastases. Regarding the number of metastatic lesions, 5 patients (35.7%) had ≤ 5 metastatic lesions, while 9 (64.3%) had more than 6, including 3 patients

(21.4%) with more than 10. [Table S1](#) summarizes the results of clinical genetic testing. Among the patients, 3 carried a pathogenic germline variant in BRCA1, and 1 exhibited a germline BRCA2 mutation. Of the remaining 10 patients without germline BRCA mutations, 1 demonstrated a somatic BRCA1 alteration. Genomic instability status (GIS) testing was performed on 10 patients, eight of whom tested positive, indicating homologous recombination deficiency (HRD). Variants in TP53 were identified across 7 archival samples, consistent with the characteristic histology of high-grade serous ovarian cancer (HGSOC). The median duration from diagnosis to study entry was 23.5 months. The median interval between the completion of the last anti-cancer treatment and the initiation of study therapy was 2.6 months. As of the data cutoff on November 10, 2024, the median follow-up period was 8.1 months, with an interquartile range (IQR) of 5.0-17.0 months.

Table 1. Demographics and baseline characteristics

Characteristic	N=14
Median age, years (range)	58.5 (43-74)
ECOG Performance Status, n (%)	
0	11 (78.6)
1	3 (21.4)
Primary tumor location, n (%)	
Ovary	12 (85.7)
Fallopian tube	2 (14.3)
High grade serous histology, n (%)	14 (100)
Residual tumor at baseline	
R0	4 (28.6)
R1	4 (28.6)
R2	1 (7.1)
Unknown	5 (35.7)
Number of prior systemic therapies (total), n (%)	
≤2	8 (57.1)
3-6	4 (28.6)
≥7	2 (14.3)
Number of prior lines of therapy for platinum-resistant recurrent disease, n (%)	
0	8 (57.1)
1	6 (42.9)
Recurrent tumor location prior to enrollment	
within the pelvic cavity	3 (21.4)
outside the pelvic cavity	6 (42.9)
distant metastasis	5 (35.7)
Number of recurrent tumor lesions	
≤5	5 (35.7)
6-10	6 (42.9)
>10	3 (21.4)
Median platinum-free interval, months (95% CI)	2.25 (1.6-4.4)
Median overall survival, months (95% CI)	9.5 (5-17.3)
Prior PARP inhibitor use, n (%)	
yes	1 (7.1)
no	13 (92.9)

Germline alterations, n (%)	
<i>BRCA1</i> pathogenic / likely pathogenic variant	3 (21.4)
<i>BRCA2</i> pathogenic / likely pathogenic variant	1 (7.1)
No germline alterations in <i>BRCA1/2</i>	10 (71.5)
Somatic alterations, n (%)	
<i>BRCA1</i> pathogenic / likely pathogenic variant	0
<i>BRCA2</i> pathogenic / likely pathogenic variant	1 (7.1)
No somatic alterations in <i>BRCA1/2</i>	7 (50.0)
Unknown	6 (42.9)
Homologous recombination deficiency status, n (%)	
Yes	8 (57.1)
No	2 (14.3)
Unknown	4 (28.6)

R0, complete resection, no macroscopic tumor; R1, optimal resection, macroscopic tumor remaining 1 cm or less; R2, suboptimal resection, macroscopic tumor residue above 1 cm; distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes, lymph nodes outside the abdominal cavity and bone); and transmural involvement of intestine.

3.2 Response to treatment

The dose-escalation trial began with three patients. Patient 1 completed the escalation phase over two cycles, while patients 2 and 3 each completed it in one cycle. During the first week (Days 1-7), patients received fuzuloparib at a dose of 150 mg BID in combination with RIF 1.62 g TID. In the second week (Days 8-14), the dosage was adjusted to fuzuloparib 150 mg BID combined with RIF 2.43 g TID. The dosage remained the same for the third week (Days 15-21), with fuzuloparib 150 mg BID and RIF 2.43 g TID. In the fourth week (Days 22-28), patients continued on fuzuloparib 150 mg BID, but RIF was paused for the week. No dose-limiting toxicities (DLTs) were observed during the trial. The ORR was 14.3% based on two patients who demonstrated partial responses according to RECIST v1.1 criteria (Figure 1A). Nine patients achieved stable disease (SD), while disease progression (PD) occurred in three patients. Of those with SD, three patients demonstrated a 20 - 30% reduction in disease burden. Based on the Gynecologic Cancer InterGroup (GCIg) criteria, a CA125 response was observed in 5 of 14 patients (35.7%), with CA125 levels decreasing by more than 50% (Figure 1B). The median PFS (mPFS) was 2.25 months (95% CI: 1.6-4.4 months; Figure 1C). The median OS (mOS) was 9.5 months, with a 95% confidence interval of 5.0-17.3 months (Figure 1D). Thirteen patients (92.9%) experienced fatal outcomes, with all deaths attributed to disease progression.

3.3 Tumor BRCA and HRR mutations

Five patients (35.7%) were identified as BRCaM based on germline and somatic BRCA gene testing, while nine (64.3%) were classified as non-BRCaM (Table 1 and S1). No significant differences were observed between these subgroups in terms of mPFS or mOS. The mPFS for the BRCaM subgroup was 2.6 months (95% CI: 0.9-6.8), compared with 2.1 months (95% CI: 1.4-2.88) in the non-BRCaM subgroup. For mOS, the BRCaM subgroup had a median of 6.7 months (95% CI: 3.9-23.9), while the non-BRCaM subgroup had a median of 12.9 months (95% CI: 5-17.3) (Figure 1E). HRD status was evaluable in 10 of 14 patients, including

8 (80.0%) HRD-positive and 2 (20.0%) HRD-negative patients. HRD status was not evaluable in the remaining 4 patients. Among the eight HRD-positive patients, the mPFS and mOS were 2.5 and 12.0 months, respectively, compared with 1.35 and 5.3 months, respectively, among the two HRD-negative patients (Figure 1F). Given the small size of the HRD-negative group, further validation in a larger cohort is warranted. One patient had received prior PARP-inhibitor therapy; following treatment with fuzuloparib plus RIF, this patient had a PFS of 2.1 months and an OS of 17.3 months.

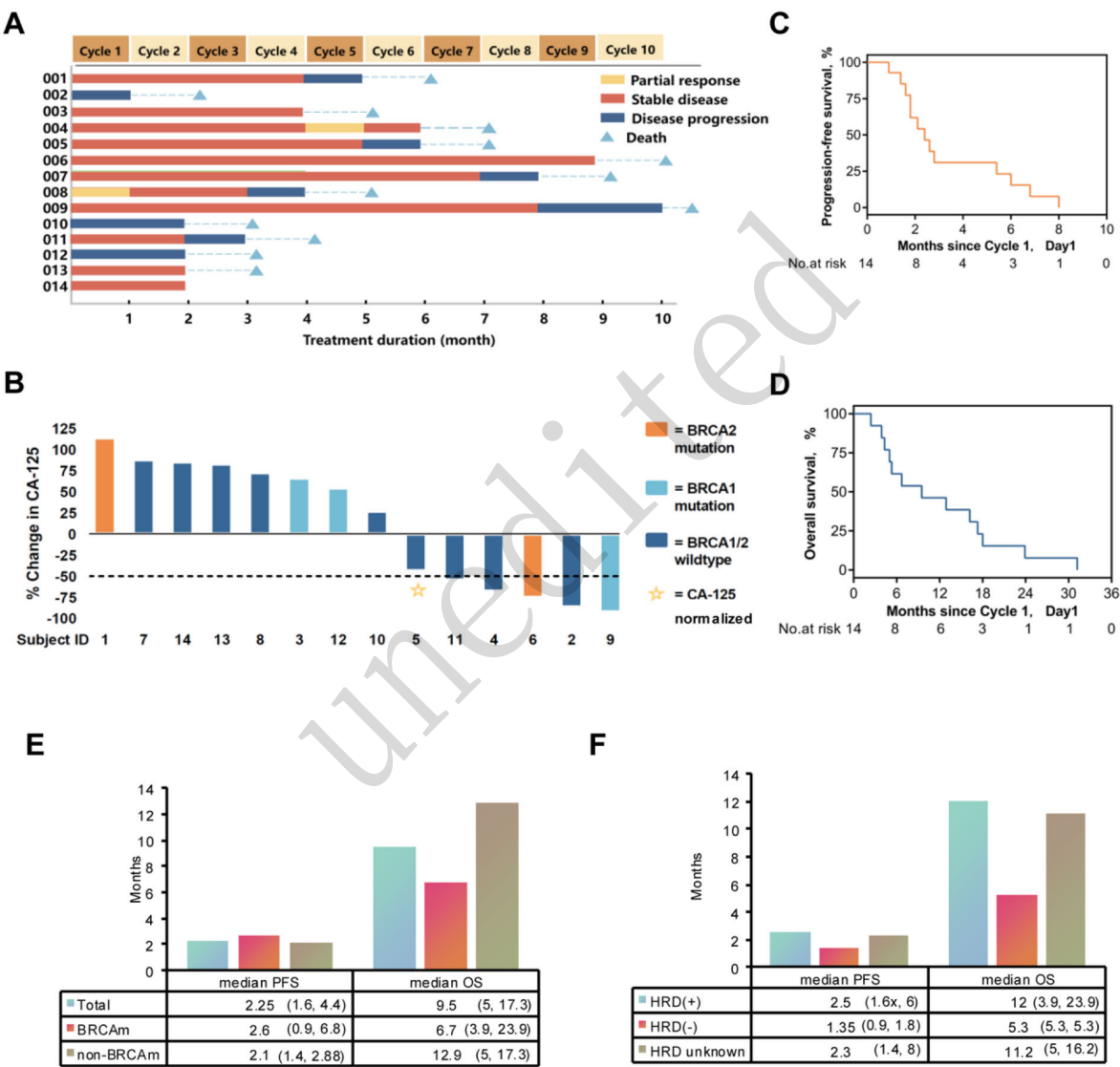


Fig 1. Clinical outcomes and biomarker associations. (A and B) Swimmer plot showing treatment duration and response for each patient (A), alongside a waterfall plot depicting the best percentage change in CA-125 from baseline (B). (C and D) Kaplan–Meier plots of progression-free survival (PFS) (C) and overall survival (OS) (D). (E and F) Impact of BRCA mutation status (E) and homologous recombination deficiency (HRD) status (F) on median PFS and OS.

3.4 Adverse events and tolerability

All 14 patients who received the combined treatment were assessed for toxicity and included in the safety analysis. Adverse events (AEs) associated with the treatment studied are presented in Table 2. The majority of AEs were classified as grade 1 or 2 and were manageable with medical intervention. Although hematological toxicities are known side effects of both fuzuloparib and RIF, only three patients experienced grade 3 hematological toxicity (all anemia). Fatigue was commonly reported, with 85.7% of patients experiencing mild to moderate fatigue (grade 1/2), and 7.1% reporting severe fatigue (grade 3). Renal dysfunction was observed in 57.1% of patients at grade 1/2 severity and in 7.1% at grade 3. Hepatic insufficiency was noted at grade 1/2 in 42.9% of patients. Gastrointestinal AEs such as nausea (grade 1/2: 35.7%; grade 3: 14.3%), vomiting (grade 1/2: 28.6%; grade 3: 7.1%), and abdominal pain (grade 1/2: 14.3%; grade 3: 7.1%) generally presented during the first cycle of treatment. Electrolyte imbalances occurred in several patients, mostly at grade 1/2, including hypokalemia, hyponatremia, and hypocalcemia; one patient experienced grade 3 hypocalcemia. In addition, one patient reported grade 1/2 hematuria. No grade 4 or 5 adverse events were observed.

Overall, 4 patients (28.6%) experienced dose interruptions, with 2 patients requiring interruptions of both drugs. The AEs leading to dose interruption of fuzuloparib or RIF included renal dysfunction (1 patient), thrombocytopenia (1 patient), nausea and vomiting with leukopenia (1 patient), and abdominal pain (1 patient). Additionally, 5 patients (35.7%) required dose reductions, including 2 patients who required reduction of both drugs. The main AEs resulting in fuzuloparib dose reductions were anemia, thrombocytopenia, and fatigue, while hepatic insufficiency, nausea and vomiting, and fatigue were the key AEs prompting RIF dose reduction.

Table 2. Summary of AEs occurring in ≥ 1 subject possibly

treatment (n=14 subjects)	G1/2 (# pts, %)	G3 (# pts, %)	Total (# pts, %)
Fatigue	12 (85.7)	1 (7.1)	13 (92.8)
Anemia	4 (28.6)	3 (21.4)	7 (50.0)
Renal dysfunction	8 (57.1)	1 (7.1)	9 (64.2)
Hepatic insufficiency	6 (42.9)	0	6 (42.9)
Nausea	5 (35.7)	0	5 (35.7)
Vomiting	5 (35.7)	0	5 (35.7)
Thrombocytopenia	4 (28.6)	0	4 (28.6)
Hypokalemia	3 (21.4)	0	3 (21.4)
Leukopenia	3 (21.4)	0	3 (21.4)
Abdominal pain	3 (21.4)	0	3 (21.4)
Hyponatremia	2 (14.3)	0	2 (14.3)
Hypocalcemia	1 (7.1)	1 (7.1)	2 (14.3)
Hematuria	1 (7.1)	0	1 (7.1)

#No grade 4-5 events occurred on study

3.5 Molecular and metabolic signatures associated with treatment response and CA125 dynamics

To explore the molecular features associated with treatment response to fuzuloparib plus RIF in patients with PROC, we performed longitudinal plasma proteomic and metabolomic profiling in 12 patients across nine treatment cycles (Supplementary Figure 1A and 1B). Treatment response was evaluated at each cycle and patients were stratified according to ORR and CA125 dynamics. Detailed proteomic and metabolomic profiling

results are provided in the supplementary materials (Supplementary Figure 1C-E). Patients in the ORR Good group showed significantly longer PFS than those in the ORR Poor group (Figure 2A). Baseline proteomic and metabolomic analyses identified distinct molecular profiles between the two groups (Figure 2B). Proteins up-regulated in the ORR Poor group were primarily associated with WNT and MAPK signaling, pyruvate metabolism, and cytochrome P450-mediated small-molecule metabolism (Figure 2C and 2D). Several proteins, including ITPR1, H2AX, ADH1B, RAC2, LDHC, and ATF2, were significantly associated with PFS (Figure 2E). Metabolomic analysis further demonstrated elevated levels of 1 metabolites linked to cytochrome P450-mediated metabolism in the ORR Poor group, with serotonin (5-hydroxytryptamine, 5-HT) emerging as a prominent metabolite interacting with multiple proteins (Figure 2F and 2G). Given its role as a pleiotropic signaling regulator, serotonin may promote tumor-cell proliferation by activating downstream MAPK signaling and related pathways (Karmakar and Lal, 2021; Zhu et al., 2022), thereby contributing to a poorer therapeutic response.

CA125 dynamics were also significantly associated with clinical outcomes, with patients in the CA125 Good group exhibiting longer PFS than those in the CA125 Poor group (Supplementary Figure 2A). Comparative proteomic and metabolomic analyses revealed distinct molecular signatures between the two groups, characterized predominantly by alterations in lipid metabolism, small-molecule metabolism, and detoxification pathways (Supplementary Figure 2B-D). Notably, UDP-glucuronosyltransferase UGT1A family members, particularly UGT1A6, were highly expressed in the CA125 Poor group, whereas multiple lysophosphatidylethanolamine (LysoPE) species were significantly elevated (Supplementary Figure 2D and 2E). Protein-metabolite interaction analysis further highlighted serotonin-associated signaling and its potential interaction with UGT1A enzymes (Supplementary Figure 2F). These findings suggested that dysregulated lipid metabolism, detoxification, and serotonin-associated signaling might contribute to unfavorable CA125 dynamics and poor treatment outcomes.

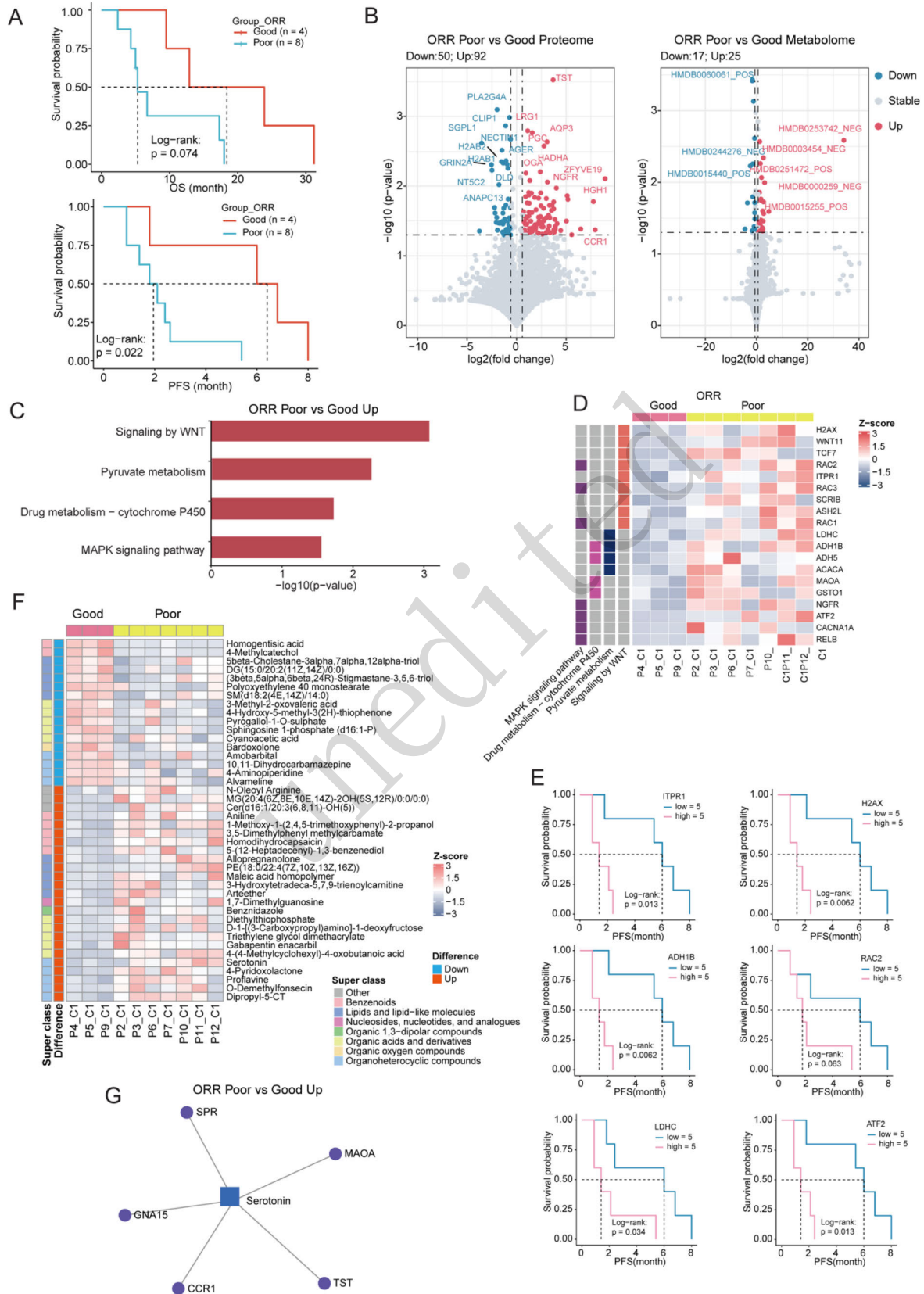


Fig 2. Differential protein and metabolite profiles associated with ORR status. (A) Kaplan–Meier survival curves showing the association between ORR grouping and overall survival (OS) and progression-free survival (PFS). (B) Volcano plot showing the differences in protein and metabolite expression levels in plasma samples at Cycle 1 between patients with good and poor ORR. (C) Bar plot showing pathway enrichment of significantly upregulated proteins in the poor ORR group. (D) Heatmap showing significantly upregulated proteins in the poor ORR group, involved in related pathways. (E). Kaplan–Meier survival curves showing proteins from panel D that were significantly negatively associated with survival outcomes. (F). Heatmap showing differentially expressed metabolites between ORR groups and the classification of these metabolites. (G). Network plot illustrating the interaction network of significantly upregulated proteins and metabolites in the poor ORR group.

3.6 Molecular and metabolic characteristics associated with BRCA and HRD status

BRCA1/2 germline mutations are established risk factors for cancer development (Tung et al., 2016; Bhaskaran et al., 2019). We first compared baseline molecular features between patients with germline BRCA1/2 mutations (BRCA Mut) and those with wild-type BRCA (BRCA WT). Differential expression analysis identified distinct proteomic and metabolomic profiles between the two groups (Supplementary Figure 3A). Proteins up-regulated in the BRCA Mut group were mainly enriched in HIF-1, VEGFA-VEGFR2, and MAPK signaling, while the corresponding metabolites were primarily associated with estrogen metabolism and fatty-acid biosynthesis (Supplementary Figure 3B-E). Estradiol emerged as a central node in the protein-metabolite interaction network (Supplementary Figure 3F), suggesting a potential role of estrogen-related signaling in the molecular characteristics of BRCA Mut patients.

We next compared baseline molecular features between HRD-positive and HRD-negative patients. HRD-positive patients exhibited distinct proteomic and metabolomic profiles, with up-regulated proteins mainly enriched in WNT, Ras, and other oncogenic signaling pathways, whereas down-regulated proteins were associated with T-cell receptor signaling and mast-cell degranulation (Figure 3A-C). Metabolomic analysis revealed alterations in beta-alanine metabolism, gluconeogenesis, branched-chain amino-acid metabolism, and tryptophan metabolism (Figure 3D and 3E). Protein-metabolite interaction analysis identified cAMP and cGMP as central nodes among up-regulated molecules, while lactate dehydrogenase B (LDHB) was a prominent node within the down-regulated network and was closely associated with pyruvate metabolism (Figure 3F). Collectively, these findings indicated that BRCA and HRD status were associated with distinct proteomic and metabolic features, involving alterations in oncogenic signaling, immune pathways, and cellular metabolism.

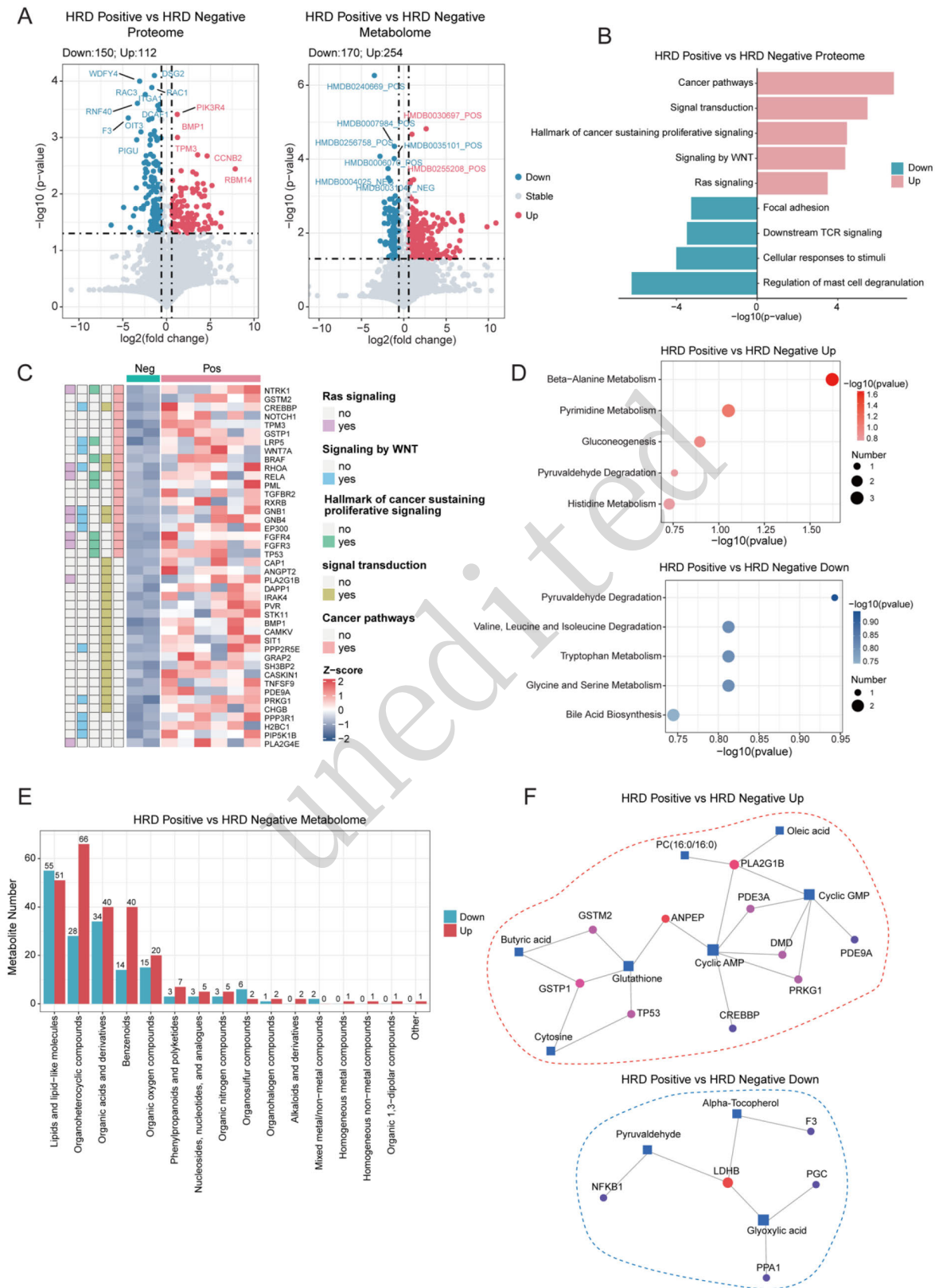


Fig. 3 HRD status shapes distinct plasma molecular landscapes. (A) Volcano plot showing the differences in protein and metabolite expression levels in plasma samples at Cycle 1 between HRD-positive and HRD-negative patients. (B) Bar plot showing pathway enrichment of significantly upregulated and downregulated proteins in the HRD-positive group. (C) Heatmap showing significantly upregulated proteins in the HRD-positive group involved in related pathways. (D) Bubble plot showing pathway enrichment of significantly upregulated and downregulated metabolites in the HRD-positive group. (E) Bar plot showing the metabolite categories that were significantly upregulated and downregulated in the HRD-positive group and the number of metabolites in each category. (F) Network plot illustrating the interaction network of significantly upregulated and downregulated proteins and metabolites in the HRD-positive group.

3.7 Time-series profiling reveals dynamic immune-metabolic programs during treatment and progression

To characterize dynamic molecular changes during treatment, we performed time-series proteomic and metabolomic profiling of sequential plasma samples from Patient 6 (three time points prior) and Patient 7 (five time points), with shared sampling points at Cycle 1, Cycle 4, and the PD event. After molecules with missing values were removed, integrated molecular profiles were clustered using the Mfuzz R package ($k = 5$). Several clusters showed concordant temporal patterns between the two patients, corresponding to early treatment (Cycle 1), mid-treatment (Cycle 4), and PD (Figure 4A and 4B). Pathway enrichment analysis revealed distinct immune and metabolic programs across treatment phases (Figure 4C and 4D). Early treatment was characterized by enhanced immune-related signaling and alterations in vitamin B6 and amino acid metabolism. At mid-treatment, proteins were primarily associated with platelet, cell-adhesion, and Ras signaling, accompanied by changes in energy metabolism. At PD, proteins were enriched in antigen presentation and phagocytosis, whereas metabolites were predominantly associated with amino-acid metabolism.

Consistent with these findings, cytokines and CD-marker profiling revealed phase-specific immune signatures (Figure 4E and 4F). Immuneactivation-associated markers, including ICOSLG, CD36, CD81, ICAM3, CD226, and CD6, showed increased expression during treatment, whereas ALCAM and ITGAM were elevated at PD. These changes suggest a shift in the immune milieu toward a potentially tumor-promoting state during disease progression. Metabolites also displayed distinct temporal patterns, with early-, mid-, and late-treatment signatures associated predominantly with vitamin B6 metabolism, selenoamino acid, and arginine/proline metabolism, respectively (Figure 4G and 4H). Collectively, these findings reveal coordinated temporal reprogramming of immune and metabolic pathways during treatment and disease progression.

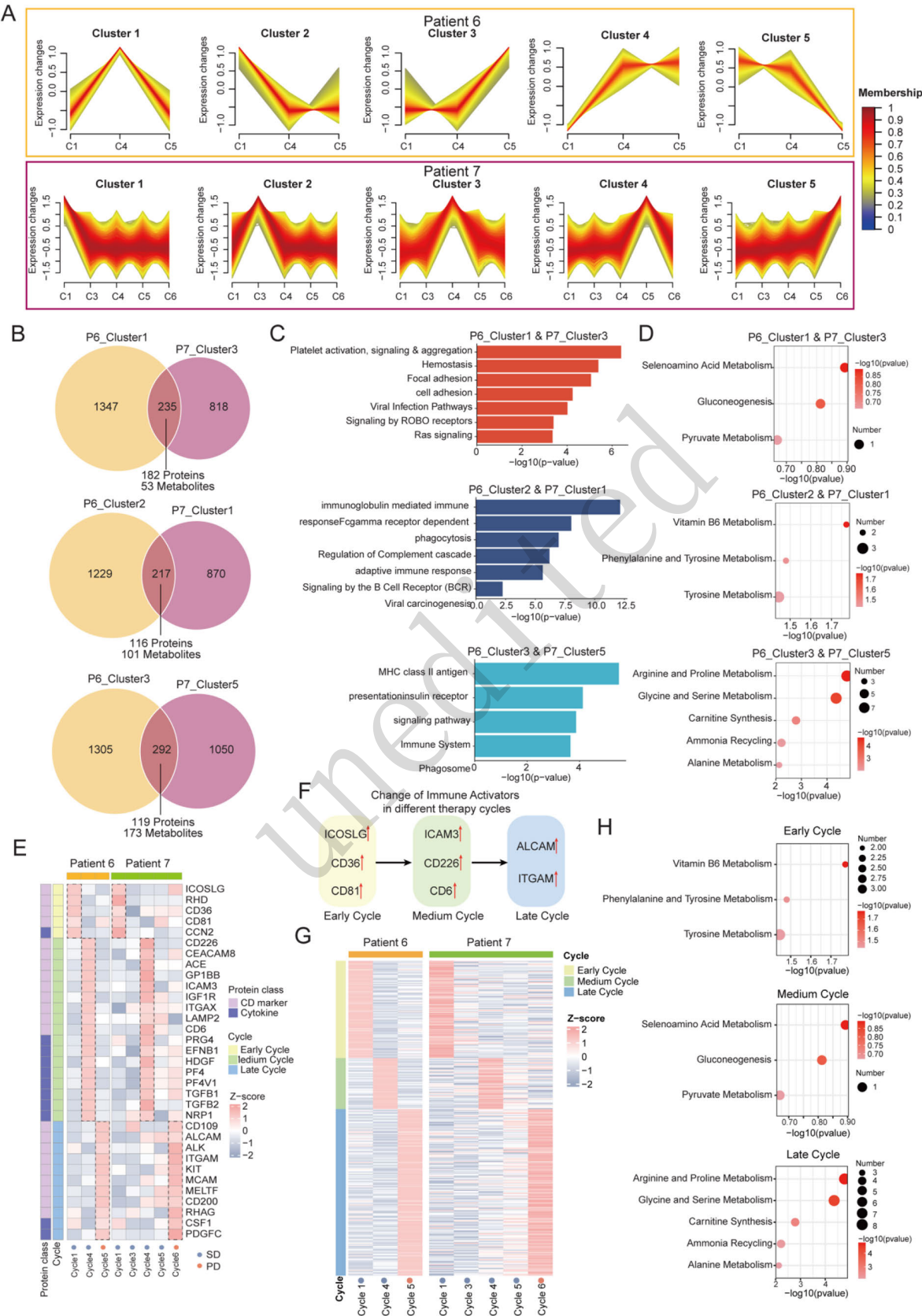


Fig. 4 Longitudinal analysis of multi-timepoint plasma samples from Patient 6 and Patient 7. (A) Patient 6 had three sampling timepoints and Patient 7 had five, with overlapping timepoints at Cycle 1, Cycle 4, and PD. Line plots showing expression trends of molecules across different temporal clusters. (B) Venn diagram showing the number of overlapping molecules in Mfuzz clusters with similar expression trends between Patient 6 and Patient 7, including: 1) P6_cluster1 and P7_cluster3 (highly expressed at Cycle 4); 2) P6_cluster2 and P7_cluster1 (highly expressed at Cycle 1); and 3) P6_cluster3 and P7_cluster5 (highly expressed at PD). (C) Bar plot showing pathway enrichment of intersecting proteins from panel B. (D) Bubble plot showing pathway enrichment of intersecting metabolites from panel B. (E) Heatmap showing CD markers and cytokines highly expressed in different cycles of Patient 6 and Patient 7, grouped as Early Cycle (Cycle 1), Med-Cycle (Cycle 4), and Late Cycle (PD: Cycle 5 for Patient 6, Cycle 6 for Patient 7). (F) Schematic illustration showing proteins related to immune activation, immune-cell recruitment, and adhesion that were highly expressed in different treatment cycles. (G) Heatmap showing metabolites with different expression levels in the early, middle, and late stages of the treatment cycle. (H) Bubble plot depicting pathway-enrichment results for metabolites significantly upregulated at different stages of treatment.

4 Discussion

In this investigator-initiated preliminary phase I/II dose-escalation and expansion study, we evaluated the safety, tolerability, and preliminary efficacy of fuzuloparib combined with RIF in patients with PROC. In this heavily pretreated population, the combination achieved an ORR of 14.3%, a disease control rate of 64.3%, an mPFS of 2.25 months, and an mOS of 9.5 months. These findings suggest preliminary antitumor activity in a clinically challenging population and provide exploratory molecular insights into treatment response and progression.

Our cohort differed from many previous PARP-inhibitor in PROC cohorts, with a high proportion of platinum-refractory disease (57.1%) and BRCA wild-type/non-BRCA-mutated tumors (64.3%), representing a population with limited treatment options and generally modest responses to PARP-inhibitor monotherapy (O'malley et al., 2023). In the CLIO/BGOG-ov10 trial, olaparib achieved an unconfirmed ORR of approximately 17.9% in PROC, with higher activity in BRCA-mutated tumors, where median PFS was 2.9 months with olaparib versus 3.8 months with chemotherapy (Vanderstichele et al., 2022). Similarly, the JAVELIN Ovarian 200 trial reported an ORR of 13.3% and mPFS of 3.7 months for avelumab plus pegylated liposomal doxorubicin (PLD) in platinum-resistant or refractory disease, without a significant benefit over PLD alone (Pujade-Lauraine et al., 2021). The QUADRA trial reported a higher ORR of 27% with niraparib in BRCA-mutated platinum-resistant/refractory ovarian cancer, whereas response rates were substantially lower in tumors without BRCA mutations or with HRD-negative/unknown status (Moore, et al., 2019). Differences across studies may reflect variations in patient characteristics, prior treatment exposure, or disease burden. Thus, the 14.3% ORR observed with fuzuloparib plus RIF provides preliminary evidence of activity in a heavily pretreated population, although the small sample size precludes definitive conclusions regarding the contribution of RIF.

The combination was generally well tolerated, with most adverse events being grade 1-2 and no grade 4/5 events. Dose interruptions and reductions were manageable, and the overall safety profile is consistent with that reported for other PARP-inhibitor-based combinations (Samol et al., 2012; Li et al., 2022; Liu et al., 2023). Careful monitoring remains important, particularly in patients with renal or hepatic dysfunction. Given our previous preclinical findings supporting antitumor activity with low-dose RIF (Xu, et al., 2021), future studies are warranted to define the optimal dose and therapeutic window of the combination. Clinical responses were

observed across BRCA status groups, and HRD-positive patients showed a trend toward longer PFS and OS than HRD-negative patients. Notably, eight of ten patients with evaluable HRD status were HRD-positive, with a median OS of 12 months. Although these subgroup findings are exploratory, they are consistent with the established association between HRD and PARP-inhibitor sensitivity (Marconato et al., 2025) and support further evaluation of HRD as a potential biomarker for patient selection. Larger prospective studies with molecular stratification are needed to determine whether RIF modifies the relationship between HRD/BRCA status and treatment response.

An important feature of this study is the integration of longitudinal plasma proteomic and metabolomic profiling. Patients with poorer ORR or unfavorable CA125 dynamics exhibited molecular signatures involving detoxification, lipid and small-molecule metabolism, and signaling pathways such as WNT and MAPK. In particular, serotonin emerges as a prominent metabolite associated with the molecular network of poor response, suggesting a potential link between metabolic adaptation and signaling regulation. These observations are consistent with previous studies implicating metabolic adaptation, drug detoxification, and bypass signaling in PARP-inhibitor resistance (Zou et al., 2025). However, given the exploratory nature of the analysis, these molecular associations should be considered hypothesis-generating rather than definitive resistance mechanisms. Longitudinal profiling reveals dynamic changes in immune and metabolic pathways during treatment and disease progression. Early treatment is characterized by immune-related signaling, whereas mid-treatment exhibits alterations in signaling, adhesion, and energy metabolism. At progression, changes in antigen presentation, phagocytosis, amino acid metabolism, and immune-related markers suggest a shift toward a potentially tumor-promoting immune milieu. These temporal changes are consistent with emerging evidence that PARP inhibition can modulate tumor-immune interactions over the course of treatment (Hockings and Miller, 2023). The concurrent changes in immune and metabolic pathways also suggest that metabolic remodeling may accompany, or potentially contribute to, immune adaptation during disease progression. Nevertheless, these observations are derived from longitudinal samples from only two patients and therefore require validation in larger cohorts.

Several limitations should be considered. The relatively small cohort size and the heavily pretreated, clinically heterogeneous population, including a high proportion of platinum-refractory and BRCA wild-type/non-BRCA-mutated patients, warrant cautious interpretation of the observed clinical outcomes. In addition, the small number of patients in the molecular subgroups limits the interpretation of subgroup findings. Overall, these preliminary results warrant further evaluation in larger prospective studies.

5 Conclusions

This study suggests that fuzuloparib combined with RIF is clinically feasible and generally tolerable, with preliminary antitumor activity in platinum-resistant ovarian cancer. Integrated proteomic and metabolomic profiling reveal metabolic reprogramming, detoxification pathways, and serotonin signaling as potential resistance mechanisms, while longitudinal profiling reveals dynamic immune-metabolic changes during treatment and disease progression. Given the small and clinically heterogeneous cohort, these findings should be considered exploratory. Further prospective studies in larger, molecularly characterized cohorts are warranted to validate these observations and investigate the potential roles of RIF and biomarkers, particularly HRD status, in treatment response.

Data availability statement

All datasets analyzed in this study are available from the corresponding author upon request.

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Author contributions

Y.S. and J.X. conceived the project. J.X., T.C., Y.Z., C.Z., S.P. and B.X. collected all clinical samples and data. S.T. and J.X. performed proteomic and metabolomic analyses. J.X., S.T., T.C., and Y.Z. conducted statistical analyses. J.X. wrote the original draft with input from all authors. J.X. and Y.S. revised the paper. Y.S. and J.X. supervised the project.

Compliance with ethics guidelines

Junfen XU, Shaoshuai TANG, Tingting CHEN, Yumei ZHOU, Changkun ZHU, Shan PAN, Bairong XIA, and Yuanming SHEN declare no conflicts of interest that pertain to this work.

The clinical trial protocol was approved by the Institutional Review Boards at both participating sites (Approval numbers: IRB-20200214-R and IRB-2023-47). All participants provided written informed consent before any study procedures were carried out. The trial is registered at Clinicaltrials.gov (NCT04518501) and was carried out in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

Declaration on the use of generative AI tools

During the preparation of this work, the authors used ChatGPT to improve language readability and check for grammatical errors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

- Barber EL, Zsiros E, Lurain JR, et al., 2013. The combination of intravenous bevacizumab and metronomic oral cyclophosphamide is an effective regimen for platinum-resistant recurrent ovarian cancer. *J Gynecol Oncol*, 24(3):258-264. <https://doi.org/10.3802/jgo.2013.24.3.258>
- Bhaskaran SP, Chandratte K, Gupta H, et al., 2019. Germline variation in brca1/2 is highly ethnic-specific: Evidence from over 30,000 chinese hereditary breast and ovarian cancer patients. *Int J Cancer*, 145(4):962-973. <https://doi.org/10.1002/ijc.32176>
- Bray F, Laversanne M, Sung H, et al., 2024. Global cancer statistics 2022: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 74(3):229-263. <https://doi.org/10.3322/caac.21834>
- Coleman RL, Oza AM, Lorusso D, et al., 2017. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ariel3): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*, 390(10106):1949-1961. [https://doi.org/10.1016/S0140-6736\(17\)32440-6](https://doi.org/10.1016/S0140-6736(17)32440-6)
- Colombo N, Sessa C, Du Bois A, et al., 2019. Esmo-esgo consensus conference recommendations on ovarian cancer: Pathology and molecular biology, early and advanced stages, borderline tumours and recurrent diseasedagger. *Ann Oncol*, 30(5):672-705. <https://doi.org/10.1093/annonc/mdz062>

- Davis A, Tinker AV, Friedlander M, 2014. "Platinum resistant" ovarian cancer: What is it, who to treat and how to measure benefit? *Gynecol Oncol*, 133(3):624-631. <https://doi.org/10.1016/j.ygyno.2014.02.038>
- Disilvestro P, Banerjee S, Colombo N, et al., 2023. Overall survival with maintenance olaparib at a 7-year follow-up in patients with newly diagnosed advanced ovarian cancer and a brca mutation: The solo1/gog 3004 trial. *J Clin Oncol*, 41(3):609-617. <https://doi.org/10.1200/JCO.22.01549>
- Gelmon KA, Tischkowitz M, Mackay H, et al., 2011. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: A phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*, 12(9):852-861. [https://doi.org/10.1016/S1470-2045\(11\)70214-5](https://doi.org/10.1016/S1470-2045(11)70214-5)
- Gonzalez-Martin A, Pothuri B, Vergote I, et al., 2019. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*, 381(25):2391-2402. <https://doi.org/10.1056/NEJMoa1910962>
- Han B, Zheng R, Zeng H, et al., 2024. Cancer incidence and mortality in china, 2022. *J Natl Cancer Cent*, 4(1):47-53. <https://doi.org/10.1016/j.jncc.2024.01.006>
- Hockings H, Miller RE, 2023. The role of parp inhibitor combination therapy in ovarian cancer. *Ther Adv Med Oncol*, 15:17588359231173183. <https://doi.org/10.1177/17588359231173183>
- Karmakar S, Lal G, 2021. Role of serotonin receptor signaling in cancer cells and anti-tumor immunity. *Theranostics*, 11(11):5296-5312. <https://doi.org/10.7150/thno.55986>
- Kaufman B, Shapira-Frommer R, Schmutzler RK, et al., 2015. Olaparib monotherapy in patients with advanced cancer and a germline brca1/2 mutation. *J Clin Oncol*, 33(3):244-250. <https://doi.org/10.1200/JCO.2014.56.2728>
- Kim G, Ison G, Mckee AE, et al., 2015. Fda approval summary: Olaparib monotherapy in patients with deleterious germline brca-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. *Clin Cancer Res*, 21(19):4257-4261. <https://doi.org/10.1158/1078-0432.CCR-15-0887>
- Konstantinopoulos PA, Matulonis UA, 2023. Clinical and translational advances in ovarian cancer therapy. *Nat Cancer*, 4(9):1239-1257. <https://doi.org/10.1038/s43018-023-00617-9>
- Ledermann JA, Raja FA, Fotopoulou C, et al., 2013. Newly diagnosed and relapsed epithelial ovarian carcinoma: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 24 Suppl 6:vi24-32. <https://doi.org/10.1093/annonc/mdt333>
- Ledermann JA, Raja FA, Fotopoulou C, et al., 2018. Newly diagnosed and relapsed epithelial ovarian carcinoma: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 29(Suppl 4):iv259. <https://doi.org/10.1093/annonc/mdy157>
- Li N, Bu H, Liu J, et al., 2021. An open-label, multicenter, single-arm, phase ii study of fluzoparib in patients with germline brca1/2 mutation and platinum-sensitive recurrent ovarian cancer. *Clin Cancer Res*, 27(9):2452-2458. <https://doi.org/10.1158/1078-0432.CCR-20-3546>
- Li N, Zhang Y, Wang J, et al., 2022. Fuzuloparib maintenance therapy in patients with platinum-sensitive, recurrent ovarian carcinoma (fzocus-2): A multicenter, randomized, double-blind, placebo-controlled, phase iii trial. *J Clin Oncol*, 40(22):2436-2446. <https://doi.org/10.1200/JCO.21.01511>
- Lindemann K, Gibbs E, Avall-Lundqvist E, et al., 2017. Chemotherapy vs tamoxifen in platinum-resistant ovarian cancer: A phase iii, randomised, multicentre trial (ovaresist). *Br J Cancer*, 116(4):455-463. <https://doi.org/10.1038/bjc.2016.435>
- Liu Y, Wang W, Yin R, et al., 2023. A phase 1 trial of fuzuloparib in combination with apatinib for advanced ovarian and triple-negative breast cancer: Efficacy, safety, pharmacokinetics and germline brca mutation analysis. *BMC Med*, 21(1):376. <https://doi.org/10.1186/s12916-023-03046-8>
- Lorusso D, Mouret-Reynier MA, Harter P, et al., 2024. Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase iii paola-1/engot-ov25 trial. *Int J Gynecol Cancer*, 34(4):550-558. <https://doi.org/10.1136/ijgc-2023-004995>
- Lou Y, Ma Y, Jin J, Zhu H, 2020. Oral realgar-indigo naturalis formula plus retinoic acid for acute promyelocytic leukemia. *Front Oncol*, 10:597601. <https://doi.org/10.3389/fonc.2020.597601>
- Ma YF, Lu Y, Wu Q, et al., 2022. Oral arsenic and retinoic acid for high-risk acute promyelocytic leukemia. *J Hematol Oncol*, 15(1):148. <https://doi.org/10.1186/s13045-022-01368-3>
- Marconato N, Tommasi O, Paladin D, et al., 2025. Unraveling homologous recombination deficiency in ovarian cancer: A review of currently available testing platforms. *Cancers (Basel)*, 17(11) <https://doi.org/10.3390/cancers17111771>
- Matulonis UA, Penson RT, Domchek SM, et al., 2016. Olaparib monotherapy in patients with advanced relapsed ovarian cancer and a germline brca1/2 mutation: A multistudy analysis of response rates and safety. *Ann Oncol*, 27(6):1013-1019. <https://doi.org/10.1093/annonc/mdw133>
- Moore K, Colombo N, Scambia G, et al., 2018. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*, 379(26):2495-2505. <https://doi.org/10.1056/NEJMoa1810858>
- Moore KN, Secord AA, Geller MA, et al., 2019. Niraparib monotherapy for late-line treatment of ovarian cancer (quadra): A multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*, 20(5):636-648. [https://doi.org/10.1016/S1470-2045\(19\)30029-4](https://doi.org/10.1016/S1470-2045(19)30029-4)
- O'malley DM, Krivak TC, Kabil N, et al., 2023. Parp inhibitors in ovarian cancer: A review. *Target Oncol*, 18(4):471-503. <https://doi.org/10.1007/s11523-023-00970-w>
- Oza AM, Tinker AV, Oaknin A, et al., 2017. Antitumor activity and safety of the parp inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic brca1 or brca2 mutation: Integrated analysis of data from study

- 10 and ariel2. *Gynecol Oncol*, 147(2):267-275. <https://doi.org/10.1016/j.ygyno.2017.08.022>
- Pujade-Lauraine E, Hilpert F, Weber B, et al., 2014. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The avelina open-label randomized phase iii trial. *J Clin Oncol*, 32(13):1302-1308. <https://doi.org/10.1200/JCO.2013.51.4489>
- Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al., 2021. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (javelin ovarian 200): An open-label, three-arm, randomised, phase 3 study. *Lancet Oncol*, 22(7):1034-1046. [https://doi.org/10.1016/S1470-2045\(21\)00216-3](https://doi.org/10.1016/S1470-2045(21)00216-3)
- Richardson DL, Eskander RN, O'malley DM, 2023. Advances in ovarian cancer care and unmet treatment needs for patients with platinum resistance: A narrative review. *JAMA Oncol*, 9(6):851-859. <https://doi.org/10.1001/jamaoncol.2023.0197>
- Samol J, Ranson M, Scott E, et al., 2012. Safety and tolerability of the poly(adp-ribose) polymerase (parp) inhibitor, olaparib (azd2281) in combination with topotecan for the treatment of patients with advanced solid tumors: A phase i study. *Invest New Drugs*, 30(4):1493-1500. <https://doi.org/10.1007/s10637-011-9682-9>
- Shoaib M, Bhutta ZA, Javed A, et al., 2025. Future of parp inhibitors in cancer treatment: Overcoming resistance and enhancing efficacy with combination therapies. *J Zhejiang Univ Sci B*, 27(1):23-43. <https://doi.org/10.1631/jzus.B2400146>
- Swisher EM, Kwan TT, Oza AM, et al., 2021. Molecular and clinical determinants of response and resistance to rucaparib for recurrent ovarian cancer treatment in ariel2 (parts 1 and 2). *Nat Commun*, 12(1):2487. <https://doi.org/10.1038/s41467-021-22582-6>
- Tang S, Shen Y, Wei X, et al., 2022. Olaparib synergizes with arsenic trioxide by promoting apoptosis and ferroptosis in platinum-resistant ovarian cancer. *Cell Death Dis*, 13(9):826. <https://doi.org/10.1038/s41419-022-05257-y>
- Torre LA, Trabert B, Desantis CE, et al., 2018. Ovarian cancer statistics, 2018. *CA Cancer J Clin*, 68(4):284-296. <https://doi.org/10.3322/caac.21456>
- Tung N, Lin NU, Kidd J, et al., 2016. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. *J Clin Oncol*, 34(13):1460-1468. <https://doi.org/10.1200/JCO.2015.65.0747>
- Vanderstichele A, Loverix L, Busschaert P, et al., 2022. Randomized clio/bgog-ov10 trial of olaparib monotherapy versus physician's choice chemotherapy in relapsed ovarian cancer. *Gynecol Oncol*, 165(1):14-22. <https://doi.org/10.1016/j.ygyno.2022.01.034>
- Xu J, Shen Y, Wang C, et al., 2021. Arsenic compound sensitizes homologous recombination proficient ovarian cancer to parp inhibitors. *Cell Death Discov*, 7(1):259. <https://doi.org/10.1038/s41420-021-00638-2>
- Yang L, Xie HJ, Li YY, et al., 2022. Molecular mechanisms of platinum-based chemotherapy resistance in ovarian cancer (review). *Oncol Rep*, 47(4) <https://doi.org/10.3892/or.2022.8293>
- Zhu HH, Huang XJ, 2014. Oral arsenic and retinoic acid for non-high-risk acute promyelocytic leukemia. *N Engl J Med*, 371(23):2239-2241. <https://doi.org/10.1056/NEJMc1412035>
- Zhu HH, Liu YR, Jia JS, et al., 2018. Oral arsenic and all-trans retinoic acid for high-risk acute promyelocytic leukemia. *Blood*, 131(26):2987-2989. <https://doi.org/10.1182/blood-2018-02-834051>
- Zhu P, Lu T, Chen Z, et al., 2022. 5-hydroxytryptamine produced by enteric serotonergic neurons initiates colorectal cancer stem cell self-renewal and tumorigenesis. *Neuron*, 110(14):2268-2282 e2264. <https://doi.org/10.1016/j.neuron.2022.04.024>
- Zou Y, Zhang H, Chen P, et al., 2025. Clinical approaches to overcome parp inhibitor resistance. *Mol Cancer*, 24(1):156. <https://doi.org/10.1186/s12943-025-02355-1>

Supplementary information

Materials and methods; Tables S1; Figs. S1-S3